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ABSTRACTS OF PAPERS AND DISCUSSION

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Hepatic Cirrhosis in Cystic Fibrosis of the Pancreas

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Small foci of biliary cirrhosis are known to occur in cystic fibrosis of the pancreas. Severe cirrhotic changes have been described in occasional cases. However, the true incidence of these lesions has been realized only recently. In addition, these changes were mostly found at autopsy and were not recognized clinically.

A group of patients in whom the lesions had progressed to a severe and distinctive type of multilobular biliary cirrhosis with portal hypertension has been recently studied in Babies Hospital. These anatomico-clinical observations prompted a survey of our autopsy material of 140 cases. An attempt was made to clarify the morphogenesis and the evolution of the liver changes.

FOCAL BILIARY CIRRHOSIS

These early and localized lesions have been observed in 32 cases and appear as small shallow stellate grooves, measuring a few millimeters in diameter. Their grayish or greenish color stands out better after formalin fixation. Their grouping and distribution are variable, though they are mostly located beneath the capsule. Late "burned out" foci appear as deep clefts. The earliest lesion was seen in a three-day old newborn with meconium ileus. Microscopically an enlarged portal space, with intact main ducts, shows numerous small ducts and cholangioles filled with inspissated eosinophilic material similar to that seen in the pancreas.

The concretions in both liver and pancreas give the same histochemical reactions. However, the material plugging the bile ductules may display a variable bile staining.

The ductules may rupture and spilling of their content in the interstitial tissue occurs. This results, whether bile is visible or not, in a massive leukocytic and histiocytic inflammation. The reticulum fibers collapse if there is necrosis of the liver cells, or may completely disappear and be replaced by granulation tissue.

The portal spaces enlarge by bile duct proliferation and progressive peripheral fibrosis. The pattern followed is that of a "trabecular" cirrhosis, typical of biliary cirrhosis.

The number of foci of biliary cirrhosis increases with the age of the patient. However, there is no simple relationship between their number, size and stage of development, and the severity of the pancreatic or pulmonary damage, and the presence or absence of hypoplasia of the gallbladder and atresia of the cystic duct. Foci at various stages of evolution are seen in the same patient and even in the same section. These findings suggest a cyclic process and the focal action of an unknown factor superimposed on an underlying diffuse physico-chemical anomaly of the secretions.

PROGRESSION TO MULTILOBULAR BILIARY CIRRHOSIS

The independent foci become joined by fine fibrous strands. Because of the initially

focal character of the lesions, cirrhotic tissue will encircle groups of preserved lobules. Secondary changes appear in the encircled lobules and, finally, a pseudo-lobular pattern develops. Seven such cases have been seen. The name of "multilobular" biliary cirrhosis with concretions has been chosen in contrast to the term "monolobular" biliary cirrhosis, as applied to the usual type of cholostatic or cholangitic cirrhosis. The three words, *multilobular, biliary,* and *concretions* define the distinctive features of the cirrhosis in fibrocystic disease of the pancreas.

MULTILOBULAR BILIARY CIRRHOSIS WITH PORTAL HYPERTENSION

Seven cases have been observed and the diagnosis has been confirmed by biopsy in five. All patients had fully manifested cystic fibrosis and symptoms of portal hypertension. The latter were the presenting symptoms in three of them. The liver was enlarged, grossly nodular and hard. The spleen was removed surgically in five cases and showed the changes characteristic of portal hypertension. The microscopic features were as follows:

1) Formation of irregular pseudolobules larger than those of typical portal cirrhosis and biliary cirrhosis, sometimes with deep clefts producing a "hepar lobatum." 2) Presence of areas of preserved lobular architecture adjacent to massive foci of bile duct proliferation with fibrosis suggesting that the lesions were initially focal. This multilobular biliary cirrhosis may be accompanied by portal lesions and changes of liver architecture by formation of pseudolobules and of regenerative nodules. 3) The presence of occasional foci of eosinophilic concretions and the absence of moderate amount of bile stasis. 4) The acute inflammation of progressive lesions.

These features distinguish them from the chronic infiltrates usually seen in portal cirrhosis of Laennec's type and from postnecrotic scarring producing the usual type of multilobular cirrhosis.

PATHOGENESIS AND ETIOLOGY

The study of morphogenesis favors the hypothesis of a primary mechanical obstruction of cholangioles and small bile ducts. The focal character of the early stage is responsible for the distinctive appearance of the cirrhosis. This picture is not duplicated by experimental or human cirrhosis induced by other known factors. Fatty metamorphosis is probably responsible for three cases of early portal cirrhosis which we have seen in cystic fibrosis of the pancreas and may be an additional factor in the etiology of multilobular biliary cirrhosis.

The rarity of this liver lesion some years ago and its increasing frequency may be due to different causes: increased life span and therefore more time to develop hepatic lesions due to focal biliary obstruction, or longer exposure to nutritional deficiency, infection or hypoxia, or injury from antibacterial agents. However, any of these single factors may be absent in individual cases. For instance, chronic infection or hypoxia were not found in two patients and furthermore were present in patients of the same age group without cirrhosis. The morphology of the liver is different from that observed in specific amino acid or protein deficiency.

Cirrhosis has not been seen in other patients receiving any of the new antibiotics for long periods of time, and therefore these do not appear to be a causative factor of cirrhosis.

The role of generalized infection and episodes of bacteremia is difficult to evaluate. It seems probable that a descending infection may enhance inflammatory changes in obstructed bile ductules.

It may be postulated that an added infection (viral hepatitis) or nutritional insult may cause an adverse response on the part of a liver which may be basically abnormal.

Age probably acts mainly by increasing the chances to develop new hepatic lesions in a progressive disease.

SUMMARY

The hepatic area must be added to the ones frequently involved in fibrocystic disease of the pancreas.

The focal hepatic lesions may progress to a pathologically distinct and widespread multilobular biliary cirrhosis with concretions. Clinically, this advanced cirrhotic process manifests itself in patients with

fibrocystic disease of the pancreas by hepatosplenomegaly, and is characterized by the symptoms of portal hypertension and by absent or only very slight icterus.

Portal hypertension may be the reason for seeking medical attention and may dominate the clinical picture.

The lesion should be known by the surgical pathologist as the liver biopsy may be an essential step of the diagnosis in some patients.*

DISCUSSION

SIGMUND L. WILENS: I am curious as to why the intraductal concretions were not bile-stained.

WILLIAM A. BLANC: The "early" concretions are usually not bile-stained. The dense concretions frequently have a faint mahogany color. The finding of true bile plugs is quite exceptional.

SIGMUND L. WILENS: Do you think that means the bile-excreting liver cells are completely destroyed before the concretions form?

WILLIAM A. BLANC: As this condition starts as a focal disease, most of the parenchyma is intact and can take care of the excretion of bile.

SIGMUND L. WILENS: Was jaundice ever a clinical manifestation?

WILLIAM A. BLANC: Not in our patients. It was reported in rare instances only and it seems most likely that the icterus of those cases was due to some superimposed condition.

SIGMUND L. WILENS: Do you think that liver punch biopsy would be a useful method of diagnosing this lesion before death?

WILLIAM A. BLANC: The diagnosis can certainly be made on a liver biopsy if this is large enough to show the typical pattern. However, both the multilobular biliary cirrhosis and the concretions should be seen before a definite diagnosis is made. When the biopsy is done during a laparotomy, we ask the surgeon to take one fragment in an area which looks relatively well preserved, and to take also a punch biopsy which will show us the changes in the central portion of the liver.

* A more complete discussion with illustrations and bibliography has been published elsewhere: di Sant'Agnese, P.E.A. and Blanc, W. A. A distinctive type of biliary cirrhosis of the liver associated with cystic fibrosis of the pancreas, *Pediatrics, 18*:387-408, 1956.

Interstitial Pneumonia in Infants

CHARLES F. BEGG and GEORGE MANI

The pathologic anatomy of interstitial pneumonia was described and the clinical aspects were briefly reviewed and correlated with morphology. The literature on the subject of interstitial pneumonia was reviewed, and etiology, pathogenesis and treatment were discussed. It was concluded that interstitial pneumonia is one of the most common causes of death in infants and that there is an urgent need for etiologic studies and an evaluation of its response to newer antibiotics.

DISCUSSION

MILTON HELPERN: I am very much interested in Dr. Begg's and Dr. Mani's paper, and I am grateful for the demonstration of these cases. I was somewhat confused by the overlap of these particular cases and some of those which in the past we used to call acute capillary bronchitis, which did have a lot of interstitial pneumonia but also bronchiolar involvement. I think this presentation tonight pretty well distinguishes these from the others. I was curious to know why